



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

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## Cryptosporidiosis (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Reduce risk of *Cryptosporidium* infection by avoiding drinking water from public swimming pools and other bodies of recreational water (AIII), touching farm animals (BIII), and having contact with known *Cryptosporidium*-infected individuals (AIII).
- Combination antiretroviral therapy (cART) to prevent or reverse severe immune deficiency is the primary modality for preventing chronic *Cryptosporidium* infection in HIV-infected children (AII\*).
- Effective cART is the primary initial treatment for *Cryptosporidium* infections in HIV-infected children and adults (AII\*).
- Nitazoxanide can be considered in immunocompromised HIV-infected children in conjunction with cART for treatment of *Cryptosporidium* infection (BII\*).
- Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (AIII).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Epidemiology

*Cryptosporidium* spp. are protozoan parasites that primarily cause enteric illness (i.e., diarrhea) in humans and animals. They have worldwide distribution and lack host specificity. The two species that infect humans most frequently are *Cryptosporidium hominis* and *Cryptosporidium parvum*. In addition, infections caused by *Cryptosporidium meleagridis*, *Cryptosporidium felis*, and *Cryptosporidium canis* have been reported in HIV-infected patients. Among HIV-infected adults, risk of morbidity associated with *Cryptosporidium* infection is greatest in those with advanced immunosuppression, typically CD4 T-lymphocyte cell (CD4) counts <100/mm<sup>3</sup>.<sup>1-3</sup> *Cryptosporidium* primarily infects the small intestine, but in immunocompromised hosts, extra-intestinal involvement has been documented.

Infection occurs after ingestion of infectious oocysts that were excreted in the feces of infected animals and humans. The parasite is highly infectious, with an ID<sub>50</sub> (median dose that will infect 50% of those exposed to the parasite) ranging from 9 to 1042 oocysts, depending on the *C. parvum* isolate,<sup>4</sup> and 10 to 83 oocysts for *C. hominis*.<sup>5</sup> Infection occurs when the ingested oocyst releases sporozoites, which attach to and invade the intestinal epithelial cells. The parasite preferentially infects the jejunum and ileum.

Contact with infected individuals (particularly diapered children or in the child care setting) or infected animals (particularly pre-weaned calves) is an important cryptosporidiosis risk factor.<sup>6,7</sup> *Cryptosporidium* oocysts can contaminate recreational water sources (such as swimming pools and lakes) and drinking water supplies and cause infection when contaminated water is ingested. Oocysts are environmentally hardy and extremely chlorine tolerant. They can persist for days in swimming pools despite standard chlorination, and typical pool filtration systems are only partially effective in removing oocysts. Multi-step treatment processes are often used to remove (i.e., filter) and inactivate (i.e., ultraviolet treatment) oocysts to protect public drinking water supplies. Foodborne transmission, particularly involving unpasteurized apple cider and ill food handlers, has been documented and individuals traveling internationally also may be at risk if they drink water in countries where water processing is not as strict as in the United States.

In a serosurvey of multiple U.S. cities, 21.3% of children aged <10 years and 21.5% of those aged 11 to 20 years had detectable response to *Cryptosporidium* antigen.<sup>8</sup> Among immunocompetent pediatric patients with diarrhea, 38% of those aged 5 to 13 years and 58% of those aged 14 to 21 years were seropositive for *Cryptosporidium* antibodies, compared with >80% of children aged 6 months to 13 years who resided near the U.S.–Mexican border and were seeking well-child care.<sup>9,10</sup> The incidence of reported cryptosporidiosis in the United States has dramatically increased since 2004, peaking at 4 cases per 100,000 people in 2007.<sup>11</sup> Cases are most frequently reported in children aged 1 to 4 years, followed by those aged 5 to 9 years. However, cryptosporidiosis is a highly underdiagnosed and underreported diarrheal illness. Infected patients can be asymptomatic, those with symptoms may not seek healthcare, healthcare providers may not request laboratory diagnostics when evaluating non-bloody diarrhea, requested ova and parasite testing may not include *Cryptosporidium* testing, and positive laboratory results are not always reported to public health officials.<sup>12</sup>

Before effective antiretroviral therapy became available, most HIV-infected patients diagnosed with cryptosporidiosis had advanced disease or AIDS. The incidence of cryptosporidiosis in HIV-infected patients has declined dramatically since the introduction of combination antiretroviral therapy (cART).<sup>13–15</sup> During the pre-cART era, the rate of cryptosporidiosis was 0.6 cases per 100 patient-years in children with a median age of 5.9 years and median CD4 count of 51/mm<sup>3</sup> who were followed on 13 Pediatric AIDS Clinical Trial Group (PACTG) protocols.<sup>16</sup> Data from the Perinatal AIDS Collaborative Transmission Study indicate that the rate of chronic intestinal cryptosporidiosis decreased from 0.2 cases per 100 person-years in the pre-cART era to 0.0 cases per 100 person-years in the post-cART era.<sup>17</sup> The PACTG estimates that the mortality rate in HIV-infected children significantly decreased from 7.2 to 0.8 per 100 person-years between 1994 and 2000 and subsequently stabilized through 2006.<sup>18</sup> The proportion of deaths due to all opportunistic infections decreased between 1994 and 2006, with declines most notable in deaths caused by *Cryptosporidium* and *Mycobacterium avium* complex (MAC).

## Clinical Manifestations

Symptoms of cryptosporidiosis develop after an incubation period of approximately 1 week (range, 2–14 days). Diarrhea—which can be profuse, usually non-bloody, and watery—and weight loss, abdominal pain, anorexia, fatigue, joint pain, headache, fever, and vomiting have been reported in immunocompetent children and adults infected with *Cryptosporidium*.<sup>19</sup> In immunocompetent hosts, illness is self-limiting, and symptoms most often completely resolve within 2 to 3 weeks. Recurrence of symptoms after seeming resolution often has been reported. Clinical presentation of cryptosporidiosis in HIV-infected patients varies with level of immunosuppression, ranging from no symptoms or transient disease to relapsing/chronic diarrhea or cholera-like diarrhea, which can lead to life-threatening wasting and malabsorption.<sup>20</sup> In immunocompromised children, chronic severe diarrhea can result in malnutrition, failure to thrive, and substantial intestinal fluid losses, resulting in severe dehydration and even death.

Different *Cryptosporidium* spp. and genotypes are associated with different clinical manifestations in children and HIV-infected adults; vomiting is associated with *C. hominis* infection in children and *C. parvum* infection in adults.<sup>21,22</sup> Neither clinical history nor physical examination allows differentiation of cryptosporidial disease from that caused by other pathogens.

Biliary tract disease is associated with CD4 counts ≤50/mm<sup>3</sup>.<sup>23</sup> Symptoms and signs include fever, right upper abdominal pain, nausea, vomiting, and elevated alkaline phosphatase. Diagnostic studies show dilatation of the common bile duct, thickening of the gall bladder wall, and pericholecystic fluid collection. Pancreatitis is rare. Although infection usually is limited to the gastrointestinal (GI) tract, respiratory cryptosporidiosis has been reported with no pathogen other than *Cryptosporidium* being detected in sputum.<sup>24,25</sup>

## Diagnosis

Healthcare providers should specifically request *Cryptosporidium* testing, because standard ova and parasite testing is unlikely to include *Cryptosporidium* spp. Performance of diagnostic tests has not been extensively

evaluated in HIV-infected children but is expected to be similar to that in HIV-uninfected children. Monoclonal antibody-based direct fluorescent antibody assay is the current test of choice for diagnosis of cryptosporidiosis because of enhanced sensitivity and specificity.<sup>26,27</sup> Antigen-detection assays that have good sensitivity and specificity are available commercially (such as enzyme-linked immunosorbent assay [EIA] and immunochromatography).<sup>28,29</sup>

Oocyst excretion can be intermittent; therefore, the parasite may not be detected in every stool, and stool specimens collected on 3 consecutive days should be examined before considering test results to be negative.<sup>30</sup> With EIA and rapid test methods, false-positive and false-negative results can occur, and confirmation by microscopy should be considered. If oocysts are not detected in stool specimens and if suspicion is high for cryptosporidiosis or limited oocyst excretion, polymerase chain reaction (PCR)-based detection is recommended because of its increased sensitivity.<sup>31</sup> PCR for *Cryptosporidium* is not commercially available; healthcare providers should contact the state health department or Centers for Disease Control and Prevention if PCR-based detection is needed. Genotyping and subtyping tools are being increasingly used to differentiate *Cryptosporidium* species in outbreak investigations and infection/contamination source tracking. *Cryptosporidium* isolates cannot be reliably genotyped/subtyped if stool is preserved in formalin.

## Prevention Recommendations

### Preventing Exposure

Caregivers and HIV-infected children should be educated and counseled about the different ways *Cryptosporidium* can be transmitted (**AIII**). Modes of transmission include having direct contact with fecal material from infected individuals (particularly children who wear diapers and infected animals), ingesting contaminated water during recreational activities, drinking contaminated water; and eating contaminated food.

Hand washing is probably the most important step to reduce the risk of *Cryptosporidium* infection (**AIII**). HIV-infected children should always wash their hands before preparing or eating food; after contact with children in diapers; after contact with clothing, bedding, toilets, or diapers soiled by someone who has diarrhea; after touching pets or other animals; and after touching anything that may have had contact with even the smallest amounts of human or animal feces (such as sand in a sandbox).

HIV-infected children should avoid contact with pre-weaned calves, ill animals, young animals (particularly dogs and cats aged <6 months and lambs), stray animals and stool from any animals or surfaces known to be contaminated with human or animal feces (**AIII**). HIV-infected children should avoid petting zoos and animal areas at farms and camps (**BIII**). After visiting an area with animals, an immunocompetent caregiver should clean the children's shoes and other surfaces that can become contaminated (such as clothes and stroller wheels).

HIV-infected children should avoid drinking water directly from ponds, streams, springs, lakes, or rivers, or swallowing water they swim or play in regardless of whether it is chlorinated (**AIII**). Caregivers and HIV-infected children should be aware that recreational water, including lakes, rivers, salt-water beaches, swimming pools, water parks, hot tubs, and interactive and ornamental water fountains may be contaminated with human or animal feces that contain *Cryptosporidium*. Note that children aged <6 years should not use a hot tub.

Some outbreaks of cryptosporidiosis have been linked to ingestion of water from contaminated municipal water supplies; the incidence of these outbreaks has dramatically decreased since the mid-1990s because of improved water treatment targeting the inactivation and removal of *Cryptosporidium*. To eliminate risk of cryptosporidiosis during outbreaks or in other situations in which a community advisory to boil water is issued, heat water used for preparing infant formula, drinking, and making ice at a rolling boil for 1 minute (**AIII**). After the boiled water cools, put it in a clean bottle or pitcher with a lid and store it in the refrigerator. Water bottles and ice trays should be cleaned with soap and water before each use. Do not touch the inside of these containers after cleaning.

Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged, non-carbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., those which can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by the user with water from a safe water source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption may be either fresh (i.e., unpasteurized) or heat-treated (i.e., pasteurized); only juices labeled as pasteurized should be considered free of risk from *Cryptosporidium*. Other pasteurized beverages, such as milk, also are considered safe to drink (**BIII**).

*Cryptosporidium*-infected patients should not work as food handlers, especially if the handled food is intended to be eaten without cooking (**AIII**).

When traveling internationally, particularly in low-resource settings, HIV-infected patients should be warned to avoid drinking tap water and not to use it to brush teeth. Ingesting ice that may be made from tap water and raw fruits and vegetables should also be avoided (**BIII**). Steaming-hot foods, self-peeled fruits, bottled and canned processed drinks, and hot coffee or hot tea are probably safe.

In a hospital, standard precautions (such as the use of gloves and hand-washing after removal of gloves) should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected individual (**AIII**). However, because of the potential for fomite transmission, some experts recommend that severely immunocompromised HIV-infected patients should not share a room with a patient with cryptosporidiosis (**CIII**). A recent report suggests that there may be potential for respiratory transmission of *Cryptosporidium*.<sup>25</sup> However, no specific modifications of current prevention efforts have been suggested.

HIV-infected adolescents who are sexually active should be counseled about avoiding sexual practices that could result in oral exposure to feces (such as oral-anal contact). To reduce the risk of exposure to feces, adolescents should use dental dams or similar barrier methods for oral-anal and oral-genital contact, wear latex gloves during digital-anal contact, and change condoms after anal intercourse. Frequent washing of hands and genitals with warm, soapy water during and after activities that could bring these body parts in contact with feces may further reduce the risk of *Cryptosporidium* infection.

## ***Preventing Disease***

Because chronic *Cryptosporidium* infection occurs most often in HIV-infected patients with advanced immunodeficiency, cART for HIV-infected children to prevent or reverse severe immune deficiency is a primary modality for prevention (**AII**).

Observational studies from the pre-cART era suggested that rifabutin or clarithromycin prophylaxis for MAC might be associated with decreased rates or risk of cryptosporidiosis.<sup>32-34</sup> However, data are conflicting and insufficient to recommend using these drugs solely for prophylaxis of cryptosporidiosis.

## ***Discontinuing Primary Prophylaxis***

Not applicable.

## **Treatment Recommendations**

### ***Treating Disease***

Immune reconstitution resulting from cART often results in clearance of *Cryptosporidium* infection. Effective cART is the primary initial treatment for these infections in HIV-infected children and adults (**AII\***).<sup>14,35</sup> *In vitro* and observational studies, some of which are case series, suggest that cART containing a protease inhibitor (PI) may be preferable because of a direct effect of the PI on the parasite.<sup>35-44</sup> PIs increase production of interferon-gamma, which in turn inhibits *Cryptosporidium* infection. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided (**AIII**).



Antimotility agents to combat malabsorption of nutrients and drugs should be used with caution (**CIII**).

No consistently effective therapy is available for cryptosporidiosis, and duration of treatment in HIV-infected patients is uncertain.<sup>45,46</sup> Multiple agents have been investigated in small randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. Azithromycin and roxithromycin have also been investigated in small open-label studies.<sup>47</sup> No pharmacologic or immunologic therapy directed specifically against *C. parvum* has yet been shown consistently effective and durable when used alone without concomitant cART.<sup>45,46</sup>

A review of clinical trials of treatment for Cryptosporidia in immunocompromised patients, including those with HIV infection, found that no agent has proven efficacy for treating cryptosporidiosis in immunocompromised patients; however, in immunocompetent individuals, nitazoxanide reduces the load of parasites. Given the seriousness of this infection in immunocompromised individuals, use of nitazoxanide can be considered in immunocompromised HIV-infected children in conjunction with cART for immune restoration (**BII\***).<sup>45,46</sup> Given that cART may directly inhibit the parasite, it is possible that the combination of cART and parasitic therapy may be synergistic.

Nitazoxanide is approved in the United States to treat diarrhea caused by *Cryptosporidium* and *Giardia lamblia* in children and is available in liquid and tablet formulations (**BI** for HIV-uninfected children and **BII\*** for HIV-infected children). An Egyptian clinical trial in 100 HIV-uninfected adults and children randomized patients to a 3-day course of nitazoxanide or placebo.<sup>48</sup> Nitazoxanide therapy reduced the duration of both diarrhea and oocyst shedding; in children, clinical response was 88% with nitazoxanide and 38% with placebo. No severe adverse events were reported, and adverse events that were reported were similar in the treatment and placebo groups in this study. A study in Zambia in 100 malnourished children (half of whom were HIV-infected) aged 12 to 35 months reported a clinical response in 56% of HIV-uninfected children treated with nitazoxanide, compared with 23% receiving placebo.<sup>49</sup> However, in the HIV-infected children, no benefit was observed from nitazoxanide (clinical response in 8% treated with nitazoxanide, compared with 25% receiving placebo). In a subsequent study of 60 HIV-infected children with cryptosporidiosis, the same investigators reported no significant benefit using twice the recommended dose administered for 28 days.<sup>50</sup> It should be noted that the children in the Zambian studies were not receiving cART. In a study in HIV-infected adults not receiving cART who had CD4 counts >50 cells/mm<sup>3</sup>, 14 days of nitazoxanide resulted in 71% (10 of 14) response using 500 mg twice daily and 90% (9 of 10) using 1000 mg twice daily, compared with 25% with placebo.<sup>51</sup> The recommended dose for children is 100 mg orally twice daily for children aged 1 to 3 years and 200 mg twice daily for children aged 4 to 11 years. A tablet preparation (500 mg twice daily) is available for children aged ≥12 years. All medications should be administered with food.

Paromomycin, a non-absorbable aminoglycoside indicated for the treatment of intestinal amoebiasis, is not approved for treatment of cryptosporidiosis. Two small, randomized trials evaluating the efficacy of paromomycin for treatment of HIV-infected patients found clinical improvement or reduced oocyst excretion in those treated with paromomycin.<sup>52,53</sup> A review of reports of paromomycin treatment in HIV-infected patients found repeated failure to cure.<sup>54</sup> Therefore, data do not support a recommendation for use of paromomycin for cryptosporidiosis (**BII\***). Clinical or parasitological cure has been documented with use of paromomycin and azithromycin in combination in case series of HIV-infected patients with cryptosporidial diarrhea and case reports of HIV-infected patients with pulmonary cryptosporidiosis.<sup>55-57</sup>

### ***Monitoring and Adverse Events, Including IRIS***

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte imbalance, malnutrition, and weight loss. In severely ill patients, total parenteral nutrition may be indicated (**CIII**). One case report describes immune reconstitution inflammatory syndrome, specifically terminal ileitis, in association with treatment of cryptosporidiosis.<sup>58</sup>

In general, nitazoxanide is well tolerated and side effects are mild, transient, and limited to the GI tract.

## ***Managing Treatment Failure***

The most important steps for managing treatment failure are optimizing cART to increase CD4 counts and providing supportive treatment (AIII).

## ***Preventing Recurrence***

No pharmacologic interventions are known to be effective in preventing recurrence of cryptosporidiosis.

## ***Discontinuing Secondary Prophylaxis***

Not applicable.

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### Dosing Recommendations for Prevention and Treatment of Cryptosporidiosis

Preventive Regimen			
Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	ARV therapy to avoid advanced immune deficiency	N/A	N/A
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	<u>Effective cART:</u> <ul style="list-style-type: none"> <li>Immune reconstitution may lead to microbiologic and clinical response</li> </ul>	<p>There is no consistently effective therapy for cryptosporidiosis in HIV-infected individuals; optimized cART and a trial of nitazoxanide can be considered.</p> <p><u>Nitazoxanide (BI, HIV-Uninfected; BII*, HIV-Infected in Combination with Effective cART):</u></p> <ul style="list-style-type: none"> <li>1–3 years: Nitazoxanide (20 mg/mL oral solution) 100 mg orally twice daily with food</li> <li>4–11 years: Nitazoxanide (20 mg/mL oral solution) 200 mg orally twice daily with food</li> <li>≥12 years: Nitazoxanide tablet 500 mg orally twice daily with food</li> </ul> <p><u>Treatment duration:</u></p> <ul style="list-style-type: none"> <li>3–14 days</li> </ul>	<p><u>Supportive Care:</u></p> <ul style="list-style-type: none"> <li>Hydration, correct electrolyte abnormalities, nutritional support</li> </ul> <p>Antimotility agents (such as loperamide) should be used with caution in young children.</p>

**Key to Acronyms:** ARV = antiretroviral; cART = combination antiretroviral therapy